632. *The Stereochemistry of the Tropane Alkaloids. Part XIV.*[1] *The Absolute Configuration of (−)-Tropic Acid, Hyoscyamine, and Hyoscine.*[2]

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The absolute configuration of (−)-tropic acid has been established by its correlation with (−)-alanine. According to the Cahn–Ingold–Prelog convention, natural tropic acid possesses the (*S*)-configuration.

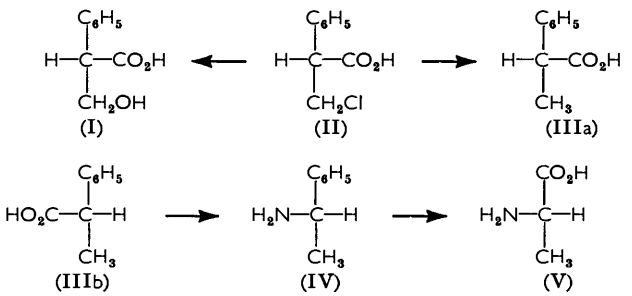
(−)-TROPIC acid is the acidic building stone of a number of important alkaloids, amongst others hyoscyamine and hyoscine. In order to obtain a deeper insight into the biosynthesis and mode of physiological action of the latter compounds, the establishment of the absolute configuration of (−)-tropic acid was necessary.

The only approach to the configuration of tropic acid reported hitherto is that by Freudenberg *et al.*,[3] based on the dextro-shift of optical rotational values observed when the acid is converted into the ester, parallel to that experienced by passing from (−)-mandelic acid and (−)-atrolactic acid to the corresponding esters. The tentative projection formula (I) for (−)-tropic acid was advanced by Freudenberg *et al.* with serious reservations: " ob derartige Schlüsse gezogen werden dürfen, und ob diese Betrachtung verallgemeinert werden darf, muss an weiterem Material geprüft werden." [3]

To check the correctness of this, the correlation of (−)-tropic acid with either (+)- or (−)-alanine was attempted.

β-Chlorohydratropic (α-chloromethyl-α-phenylacetic) acid (II) was resolved by McKenzie and Strathern [4] more than three decades ago, and the lævorotatory acid was subsequently hydrolysed to (−)-tropic acid (I), the reaction being accompanied by slight racemization; hydrolysis with aqueous ammonia gave (−)-tropamide in a higher state of optical purity.

On the other hand, (+)-α-phenylpropionic acid (IIIb) was subjected to the Curtius reaction, to give (−)-1-phenylethylamine [5] (IV), and the *N*-benzoyl derivative was oxidized, in turn,[6] to (+)-alanine (V).



Since the Curtius method involves a 1,2-carbanion shift, and proceeds, with the exception of a single case,[8] with retention of configuration [7,11] within the migrating group, the correlation of (+)-α-phenylpropionic acid (IIIb) with natural (+)-alanine can be regarded as decisive.

[1] Part XIII, preceding paper.
[2] Preliminary communication, *Tetrahedron Letters*, 1959, No. 7, 16.
[3] Freudenberg, Todd, and Seidler, *Annalen*, 1933, **501**, 206.
[4] McKenzie and Strathern, *J.*, 1925, **127**, 86.
[5] Bernstein and Whitmore, *J. Amer. Chem. Soc.*, 1939, **61**, 1324.
[6] Leithe, *Ber.*, 1931, **64**, 2827.
[7] Alexander, " Principles of Ionic Organic Reactions," Chapman and Hall, London, 1950, p. 118.
[8] Skita and Rössler, *Ber.*, 1939, **72**, 461.

In consequence, according to the convention of Cahn *et al.*,[9] (+)-α-phenylpropionic acid is designated as (*S*) (IIIb), whilst the (*R*)-configuration corresponds to the lævorotatory form (IIIa).

The single missing link between tropic acid and alanine was now the correlation of (—)-β-chlorohydratropic acid (II) with either (*S*)- or (*R*)-α-phenylpropionic acid. This work has been completed recently in the authors' laboratory.

β-Chlorohydratropic acid, obtained from atropic acid,[10] was resolved, with codeine in place of the morphine used by McKenzie *et al.*[4] The lævorotatory acid, m. p. 62°, gave correct rotational values. Hydrogenolysis of this compound over palladized charcoal in ethyl acetate, in the presence of barium hydroxide, resulted in the formation (*R*)-(—)-α-phenylpropionic acid. The Cahn–Ingold–Prelog convention [9] then gives the configuration (*S*)-(—)-tropic acid (I) for the lævorotatory form.

Experimental

(±)-β-*Chlorohydratropic* (α-*Chloromethyl-α-phenylacetic*) *Acid* (II).—This was prepared essentially by the method of McKenzie and Wood [10] by passing dry hydrogen chloride into atropic acid (6·1 g., 0·041 mol.) in dry ether (122 ml.) for 6 hr. at 25°. The ethereal solution was washed with water and dried ($CaCl_2$), and the solvent removed, to give crystals (6·9 g., 90·8%), m. p. 86—88°.

Resolution. Codeine (6·34 g., 0·0212 mol.) and (±)-β-chlorohydratropic acid (2·7 g., 0·0147 mol.) were dissolved separately in methanol (30 ml. each), the solutions were mixed at 65°, and the mixture was kept for 2 days at 60°. Filtration then afforded crystals (4 g.) of codeine (—)-β-chlorohydratropate, which, after being boiled with methanol (50 ml.), gave a pure product, m. p. 138° (decomp.), $[\alpha]_D^{20}$ −95° (*c* 0·4 in methanol) (Found: C, 67·9; H, 6·3; N, 2·7. $C_{27}H_{30}ClNO_5$ requires C, 67·0; H, 6·2; N, 2·9%).

This salt was treated with 10% hydrochloric acid (70 ml.) and then extracted several times with ether (total 250 ml.). The combined ethereal extracts were washed with water, dried ($CaCl_2$), and evaporated. The residual crystals (0·8 g., 59·2%) had m. p. 62°, $[\alpha]_D^{20}$ −115° (*c* 0·3 in ethanol). McKenzie and Wood [10] reported m. p. 62°, $[\alpha]_D^{20}$ −115° (*c* 0·4 in methanol).

Hydrogenolysis of (—)-β-*Chlorohydratropic Acid to* (—)-α-*Phenylpropionic Acid.*—Barium hydroxide dihydrate (2 g., 0·00965 mol.) and 10% palladized charcoal (0·5 g.) were shaken in ethyl acetate (60 ml.) in a hydrogen atmosphere. After the uptake of hydrogen by the catalyst had ceased, (—)-β-chlorohydratropic acid (0·44 g., 0·002375 mol.) in ethyl acetate (40 ml.) was added and the mixture hydrogenated at 26°/1 atm. When absorption (60 ml.; calc., 55·5 ml.) was complete, the solution was acidified with 5N-hydrochloric acid to pH 1 and filtered. The filtrate was evaporated to dryness and the residual oil distilled *in vacuo*. The distillate (0·2 g., 56·2%) had b. p. 115°, $[\alpha]_D^{20}$ −76° (*c* 0·79 in 96% ethanol) (Found: C, 72·2; H, 6·7. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%).

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[9] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[10] McKenzie and Wood, *J.*, 1919, **115**, 828.
[11] Arcus and Kenyon, *J.*, 1938, 485.